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TRASK BRITT
P.O. BOX 2550
SALT LAKE CITY, UT 84110

EXAMINER	
BELYAVSKYI, MICHAIL A	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/780,205
Filing Date: February 09, 2001
Appellant(s): WOUTERS ET AL.

Andrew F.Nilles
For Appellant

SUPPLEMENTAL EXAMINER'S ANSWER

This is in response to the "ORDER RETURNING UNDOCKETED APPEAL TO EXAMINER", mailed on 12/06/05.

In the " ORDER RETURNING UNDOCKETED APPEAL TO EXAMINER" it has been stated that the matters requiring attention prior to docketing are:

- listing of the references applied in the Examiner's Answer does not appear under the required heading of Evidence relied upon.
- no indication on the record that the Appeal Brief fee has been collected.

With regards to the first matter:

Listing of the references applied in the Examiner's Answer now appear under the heading of Evidence Appendix.

With regards to the second matter:

The Appeal Brief fee has been collected on 12/09/05 as indicated now on record.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the Brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The statement of the status of the claims contained in the brief is correct.

The amendment after final rejection filed on October 8, 2004 has been entered.

(5) Summary of claimed subject matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of rejection to be review on appeal

The appellant's statement of the grounds of rejection to be review on appeal in the brief is correct.

Issue I. Enablement/35 U.S.C. 112, first paragraph

Claims 2, 9, 10, 13-22, 24, 27-31, 35 and 40, 42- 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody or fragment thereof and composition comprising said antibody or fragments which binds to an epitope and broken from an epitope under specifically chosen conditions recited in Table 1 that binds to a dye and detects the plaque and suitable for detection of dental plaque or other oral pathogens does not reasonably provide enablement for an antibody or fragment thereof which binds to en epitope and broken from an epitope under broadly recited conditions that is capable of use in any therapeutic or any cosmetic treatment of externally accessible parts of the human or the animal body.

Appellant has not provided sufficient guidance to enable one skill in the art to use an antibody or fragment thereof which binds to en epitope and broken from an epitope under broadly recited conditions other than under specifically chosen conditions recited in Table 1. The amended claim 40 still recited condition wherein antibody binds to an epitope at pH of 8.5 and broken at 7.0. Said condition are not the one as recited in Table 1. Appellant himself acknowledge that the specification disclosed only 16 specific clones out of the entire phage display library, which includes at the very least, millions of candidate monoclonal antibodies, that possess the required specific characteristics as recited in Table 1, selection A to D. For example, the selection C, requires that antibody binds to epitope at specific pH of 8.5 and 1M NaCl and is broken at pH of 7.0. In other word out of millions monoclonal antibody only 16 monoclonal antibody were capable to bind to epitope and be broken from epitope at very specific set of conditions for example at condition C antibody binds to epitope at specific pH of 8.5 and 1M NaCl and broken from epitope at pH of 7.0. Clearly said conditions are differ from recited conditions in claim 40. It is the Examiner position that the specification lack of sufficient guidance and predictability in determining on how to make and use an antibody or fragments thereof that able

to bind to and broken from an epitope under any broadly recited conditions, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. In addition, Simonson et al., (US Patent 4,138,476) teach that the ability of antibody-enzymes complex to be retain in the oral cavity depends on pH and in oral fluids is vary from 5.4 to 7.8 and can be diminished by the tendency for the pH of the oral fluid to rise to the 6.2 to 7.4 range. (see entire document, column 1, lines 55-67 and column 2, lines 5-10 in particular). In addition, Weir ed. (Immunochemistry, Volume 1, 1986, p38.1-38.15 Blackwell Scientific Publication, Oxford) teaches that ability of antibody and fragment thereof to bind to and eluted from an epitope is unpredictable and varies depending on pH and ion strength (see pages 38.5-38.6 in particular).

Also an issue is that Appellant himself acknowledge that the ability of an antibodies to be broken from an epitope at any desired moment can be of benefit only for removing the dye which are used for the detection of dental plaque or other oral pathogens, without lips, tongue and gums remained colored for a long time (Page 2, lines 19-34 of the specification as filed). The specification as filed does not adequately teach what other benefits of the antibody or fragments thereof that are capable of binding to therapeutically or cosmetically or diagnostically active substance and able to bind to and broken from an epitope u under specifically chosen condition would be. Moreover, Simonson et al., (US Patent 4,138,476) teach that the longer the antibody-enzyme complex bound to en epitope the better the therapeutic outcome would be (see Abstract in particular). Thus, Appellant has not provided sufficient guidance to enable one skill in the art to use an antibody or fragment thereof which binds to en epitope and broken from an epitope under broadly recited conditions that is capable of use in any therapeutic or any cosmetic treatment of externally accessible parts of the human or the animal body other than antibody or fragment thereof and composition comprising said antibody or fragments which binds to an epitope and broken from an epitope under specifically chosen conditions recited in Table 1 that binds to a dye and detects the plaque and suitable for detection of dental plaque or other oral pathogens.

Issue II. Rejection under 35 U.S.C. 103(a)

1. Claims 2, 9, 10, 13-22, 28, 30-31, 35, 40, and 42-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beggs et al., (US Patent NO: 5,490,988) in view of Goding (Monoclonal Antibodies; Principles and Practice, 1983, Academic. Press, New York. see entire book, particularly pages 44-45)

Beggs et al, teach an antibody and antibody fragment, comprising F (ab) or Fv fragments that are able to bind to a target site through antibody –antigen binding at conditions lie within physiologically acceptable limits (see entire document , column 1, lines 39-41 and column 2, lines 18-20 in particular). pH of between 6 and 8 would be considered by one of ordinary skill in the art to lie within physiological limits. Beggs et al., further teach that antibody or antibody fragment is capable of use in a target or temporally diagnostic of externally accessible parts of a human body, particularly bind to an antigenic component of dental plaque under physiologically acceptable limits (see column 4, lines 16-30 in particular). Beggs et al., also teach that the antibody or fragment thereof binds therapeutic active agent, wherein therapeutic agent comprises an enzyme (see column 5, lines 19-42. in particular). The antibody fragment is a fragment of an antibody to *Streptococcus. mutans* and the therapeutic agent is glucose oxidase (column 4, lines 22-27 in particularly). Begges et al., also teach that the antibody or fragment thereof will be used to detect plaque in oral cavity or capable of bleaching teeth (column 4, lines 25-60 in particular). Beggs et al., also teach that antibody and the therapeutic agents are incorporated in one or more pharmaceutically acceptable dilutent or carrier (column 5, lines 44-46 in particular). Beggs et al., also teach composition useful as a teeth cleaning agent, mouthwash, toothpaste comprising antibody or fragment thereof (column 5, lines 65-67 and column 6, lines 1-6 in particular).

Beggs et al do not explicitly teach that bounds between antibody or fragment thereof and antigen can be broken under specifically chosen conditions.

Goding teaches that during optimization of each purification protocol for each antibody of interest and a fragment thereof, the parameters such as pH and ionic strength play an essential role and that it is an inherent properties of all antibody and fragment to bind to an epitope under

one set of specifically chosen conditions and be eluted from an epitope (bound of antibody to an epitope is broken) under specifically chosen different conditions (pages 44-45 in particularly).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to determine all operable and optimal rangers of pH and ion strength at which antibody or fragment thereof binds to and eluted from an epitope, as taught by Goding and use it for antibody or fragment thereof taught by Beggs et al. Thus, independent claim 40 and dependent claims 2, 9, 10, 13-22,24, 27-30 35, 43 and 44 are obvious over the prior art of Beggs et al., and Goding. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

2. Claims 2, 9, 10, 13-21, 24, 27, 28, 30, 31, 35, 40 and 42-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cummins et al.,(EP 0736544) in view of Goding

(Monoclonal Antibodies; Principles and Practice, 1983, Academic. Press, New York. see entire book, particularly pages 44-45).

Cummins et al. teach an monoclonal antibody and fragment thereof to salivary peliicle, which are capable of recognizing cryptitopes . These antibody and fragment thereof are particularly suitable to treat oral cavity (see entire document, Abstract in particular). Cummins et al. teach various binding conditions that lie within physiologically acceptable limits, including pH and ion strength (page 4, lines 38-40 in particular). pH of between 6 and 8 would be considered by one of ordinary skill in the art to lie within physiological limits. Cummins et al. also teach that antibody and fragment thereof binds diagnostically, therapeutically or cosmetically active substance (see Abstract and pages 3-4 in particular) and can be visualized by using fluorescent labeled antibodies (page 11 in particular). Cummins et al., teach a composition comprising at least one antibody and physiologically acceptable dilutent that is useful as a cleaning agent (see Example 5 in particular) Cummins et al., teach that diagnostically, therapeutically or cosmetically active substance comprises enzyme such as a proteases, including papain, pepsin, trypsin, ficin and bromelin (page 3, lines 35-55 in particular). Cummins et al. teach the antibody or fragment thereof is capable of binding an epitope of a pathogenic micro-organism (page 3, lines 1-5 in particular) and can be used for teeth bleaching (page 3, lines 3-5 in particular).

Cummins et al. do not explicitly teach that bounds between antibody or fragment thereof and antigen can be broken under specifically chosen conditions.

Goding teaches that during optimization of each purification protocol for each antibody of interest and a fragment thereof, the parameters such as pH and ionic strength play an essential role and that it is an inherent properties of all antibody and fragment to bind to an epitope under

one set of specifically chosen conditions and be eluted from an epitope (bound of antibody to an epitope is broken) under specifically chosen different conditions. (pages 44-45 in particularly). It would have been obvious to one of ordinary skill in the art at the time the invention was made to determine all operable and optimal rangers of pH and ion strength at which antibody or fragment thereof binds to and eluted from an epitope, as taught by Goding and use it for antibody or fragment thereof taught by , Cummins et al. Thus, contrary to Appellant' s assertion it is the Examiner position that independent claim 40 and dependent claims 2,9,10, 13-22, 24, 27-30 35, 43 and 44 are obvious over the prior art of Cummins et al. and Goding. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

3. Claim 29 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Beggs et al., (US Patent NO: 5,490,988) in view of Goding (Monoclonal Antibodies; Principles and Practice, 1983, Academic. Press, New York. see entire book, particularly pages 44-45) as applied to

claims 2, 9, 10, 13-22, 28, 30-31, 35, 40, and 42-49 as above, and further in view of Cole et al., (Immunol. &Infect. Diseases 1993, 3, 33-35)

The teachings of Beggs et al., and Goding have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of an antibody capable of binding *Porphyromonas gingivalis*.

Cole et al., teach an antibody to *Porphyromonas gingivalis* (see entire document, Abstract in particular) . Cole et al., further teach that this antibody play essential role in the immunopathology of periodontal disease.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the teaching of Cole et al., and those of Beggs et al., and substitute antibody capable of binding to one pathogenic micro-organism associated with periodontal disease with antibody capable of binding with another pathogenic micro-organism associated with periodontal disease.

One of ordinary skill in the art at the time the invention was made would have been motivated do so, because antibody to *Porphyromonas gingivalis* are essential in the immunopathology of periodontal disease and could be used to delivery of the therapeutic agents to the target site as taught by Beggs et al.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

4. Claim 43 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Beggs et al., (US Patent NO: 5,490,988) in view of Goding (Monoclonal Antibodies; Principles and Practice, 1983, Academic. Press, New York. see entire book, particularly pages 44-45) as applied to claims 2, 9,10, 13-22, 28, 30-31, 35, 40, and 42-49 as above, and further in view of Fischer (US Patent 5,571,511).

The teachings of Beggs et al., and Goding have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of an antibody capable of binding *Staphylovovvus epidermidis.*

US Patent '511 teach an antibody to *Staphylococcus epidermidis* (see entire document, Abstract in particular) . US Patent '511 further teach that this antibody play essential role in the new therapy for treatment of Staphylococcus infection (see column 4, lines 31-35 in particular

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '511 and those of Beggs et al., and substitute antibody capable of binding to one pathogenic micro-organism associated with periodontal disease with antibody capable of binding with another pathogenic micro-organism associated with periodontal disease.

One of ordinary skill in the art at the time the invention was made would have been motivated do so, because antibody to *Staphylococcus epidermidis* play essential role in the new therapy for treatment of Staphylococcus infection and could be used to delivery of the therapeutic agents to the target site as taught by Beggs et al.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(7) Response to Argument

Issue I. Enablement/35 U.S.C. 112, first paragraph

1. Claims 2, 9, 10, 13-22, 24, 27-31, 35 and 40, 42- 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody or fragment thereof and composition comprising said antibody or fragments which binds to an epitope and broken from an epitope under specifically chosen conditions recited in Table 1 that binds to a dye and detects the plaque and suitable for detection of dental plaque or other oral pathogens does not reasonably provide enablement for an antibody or fragment thereof which binds to en epitope and broken from an epitope under broadly recited conditions that is capable of use in any therapeutic or any cosmetic treatment of externally accessible parts of the human or the animal body.

At page 6 of the Brief, Appellant argues that as filed specification disclosed a working example of a selected monoclonal antibody or fragment having the binding characteristics as recited in amended claim 40. For example

clone 3 is able to bind to and disassociate from an epitope under the selected conditions of B , C and D, thereof claim 40 enable by the as filed specification.
At pages 7 -14 of the Brief, Appellant asserts that dependent claims 43, 2,9, 10,13,14, 15, 16, 17-22, 24 ,27-31 and 35 are dependent from the base claim 40 and thus should be also enabled.

At page 13 of the Brief, Appellant asserts that claim 42 and dependent claims 45-49 should be enable since as filed the specification disclosed multiple working examples that satisfy the condition of selection D.

Contrary to Appellant's assertion, it is noted that condition recited in the amended claim 40, i.e. binding under pH.8.5 and elution under p 7.0 does not correspond to any of the condition B, C or D as disclosed in Table 1, of the Specification as filed. For example, the selection C, requires that antibody binds to epitope at specific **pH of 8.5 and 1M NaCl and is broken at pH of 7.0.** Appellant himself acknowledge that the specification disclosed only 16 specific clones out of the entire phage display library, which includes at the very least, millions of candidate monoclonal antibodies, that possess the required specific characteristics as recited in Table 1, selection A to D. In other word out of millions monoclonal antibody only 16 monoclonal antibody were capable to bind to epitope and be broken from epitope at very specific set of conditions for example at condition C antibody binds to epitope at specific pH of 8.5 and 1M NaCl and broken from epitope at pH of 7.0. Clearly said conditions are differ from recited conditions in claim 40. It is the Examiner position that the specification lack of sufficient guidance and predictability in determining on how to make and use an antibody or fragments thereof that able to bind to and broken from an epitope under any broadly recited conditions, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. In addition, Simonson et al., (US Patent 4,138,476) teach that the ability of antibody-enzymes complex to be retain in the oral cavity depends on pH and in oral fluids is

vary from 5.4 to 7.8 and can be diminished by the tendency for the pH of the oral fluid to rise to the 6.2 to 7.4 range. (see entire document, column 1, lines 55-67 and column 2, lines 5-10 in particular). In addition, Weir ed. (Immunochemistry, Volume 1, 1986, p38.1-38.15 Blackwell Scientific Publication, Oxford) teaches that ability of antibody and fragment thereof to bind to and eluted from an epitope is unpredictable and varies depending on pH and ion strength (see pages 38.5-38.6 in particular).

With regards to Appellant's assertion that claim 42 and dependent claims 45-49 should be enable since as filed the specification disclosed multiple working examples that satisfy the condition of selection D. The issue raised by the Examiner with regard to said claims was about what benefits of said antibody or fragments thereof that are capable of binding to and broken from an epitope under specifically chosen condition would be other than being suitable for targeting and local administration of active substances for therapeutic treatment of infections in the oral cavity. Appellant himself acknowledge that the ability of an antibodies to be broken from an epitope at any desired moment can be of benefit only for removing the dye which are used for the detection of dental plaque or other oral pathogens, without lips, tongue and gums remained colored for a long time (Page 2, lines 19-34 of the specification as filed). The specification as filed does not adequately teach what other benefits of the antibody or fragments thereof that are capable of binding to therapeutically or cosmetically or diagnostically active substance and able to bind to and broken from an epitope u under specifically chosen condition would be. Moreover, Simonson et al., (US Patent 4,138,476) teach that the longer the antibody-enzyme complex bound to en epitope the better the therapeutic outcome would be (see Abstract in particular). Thus, Appellant has not provided sufficient guidance to enable one skill in the art to use an antibody or fragment thereof which binds to en epitope and broken from an epitope under broadly recited conditions that is capable of use in any therapeutic or any cosmetic treatment of externally accessible parts of the human or the animal body other than antibody or fragment thereof and composition comprising said antibody or fragments which binds to an epitope and broken from an epitope under specifically chosen conditions recited in Table 1 that binds to a dye and detects the plaque and suitable for detection of dental plaque or other oral pathogens.

It is noted that Appellant has not addressed this issue.

Issue II: Rejection under 35 U.S.C. 103(a)

1. At page 15 of the Brief, Appellant argues that although Beggs et al., teach a physiologically acceptable limits of pH between 6 and 8, a binding pH of 8.5 as recited in the claim 40 does not fall within the physiologically acceptable limits. Appellant further asserts that Beggs et al., does not mention that bound between antibody or fragment thereof is broken at pH of 7.

At page 16 of the Brief, Appellant asserts that Goding reference does not refer to the antibodies of Beggs et al., thus the cited references cannot established that the antibody of Beggs et al necessary disassociate at a pH of 7. Appellant further asserts that one of ordinary skill in the art would not reasonable expect the antibodies of Beggs et al., which binds at physiological conditions to dissociate at pH of about 7.0 and further that there is no suggestion or motivation to combine the cited references.

At page 17 of the Brief, Appellant asserts that since dependent claims 2, 9 10, 13-22, 28, 30-31, 35 and 43-44 include the elements of independent claim 40 and a prima facie case of obviousness cannot be established with regard to claim 40, a prima facie case of obviousness also cannot be established with regards to any of said dependent claims.

Appellants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Appellant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This appellant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

In response to appellant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). Moreover, it is noted that Beggs et al., do not set a range of physiologically acceptable limits of pH to be between 6 and 8. Beggs et al, teach an antibody and antibody fragment, comprising F (ab) or Fv fragments that are able to bind to a target site through antibody –antigen binding at conditions lie within physiologically acceptable limits (see entire document , column 1, lines 39-41 and column 2, lines 18-20 in particular). It is the examiner position, that one skill in the art would consider pH of 8.5 to lie within physiological limits. Beggs et al., further teach that antibody or antibody fragment is capable of use in a target or temporally diagnostic of externally accessible parts of a human body, particularly bind to an antigenic component of dental plaque under physiologically acceptable limits (see column 4, lines 16-30 in particular). Beggs et al., also teach that the antibody or fragment thereof binds therapeutic active agent, wherein therapeutic agent comprises an enzyme (see column 5, lines 19-42. in particular). The antibody fragment is a fragment of an antibody to *Streptococcus. mutans* and the therapeutic agent is glucose oxidase (column 4, lines 22-27 in particularly). Begges et al., also teach that the antibody or fragment thereof will be used to detect plaque in oral cavity or capable of bleaching teeth (column 4, lines 25-60 in particular). Beggs et al., also teach that antibody and the therapeutic agents are

incorporated in one or more pharmaceutically acceptable dilutent or carrier (column 5, lines 44-46 in particular). Beggs et al., also teach composition useful as a teeth cleaning agent, mouthwash, toothpaste comprising antibody or fragment thereof (column 5, lines 65-67 and column 6, lines 1-6 in particular).

Beggs et al., do not explicitly teach that bounds between antibody or fragment thereof and antigen can be broken under specifically chosen conditions as recited in claims 40 or 42.

Goding teaches that during optimization of each purification protocol for each antibody of interest and a fragment thereof, the parameters such as pH and ionic strength play an essential role and that it is an inherent properties of all antibody and fragment to bind to an epitope under one set of specifically chosen conditions and be eluted from an epitope (bound of antibody to an epitope is broken) under specifically chosen different conditions. (pages 44-45 in particularly). The examiner disagrees with Appellant's assertion that one skill in the art would not expect that antibody of Beggs et al., would be eluted at pH 7.0. As taught by Goding, it was well known in the art at the time the invention was made , that various elution buffers with various pH including elution with water, i.e. with pH about 7.0 should be used. Moreover, to preserve the structure of antibody-antigen complex during elution process gentle rather harsh elution condition should be used. Clearly, one skill in the art would consider elution with pH of 7.0 to be a gentle condition. It would have been obvious to one of ordinary skill in the art at the time the invention was made to determine all operable and optimal rangers of pH and ion strength at which antibody or fragment thereof binds to and eluted from an epitope, as taught by Goding and use it for antibody or fragment thereof taught by Beggs et al. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

With regards to the claims 2, 9 10, 13-22, 28, 30-31, 35 and 43-44. As has been discussed supra, it is the Examiner position that claim 40 is *prima facie* obviousness in view of the prior art references of record. Thus for at least the same reasons as base claim 40, said claims are also *prima facie* obvious.

At page 18 of the Brief, Appellant argues about dependent claim 26.

It is noted however, that said claim has been withdrawn from the consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

At page 20 of the Brief, Appellant argues that claim 42 is directed towards a selected monoclonal antibody or fragment thereof having specific binding characteristics, not to a method of determining or selecting all operable and optimal ranges of Ph and ion strength which are not disclosed in Beggs et al., alone or in a combination with Goding.

Contrary to Appellant's assertion the issue raised by the Examiner in rejected said claims was not about determining or selecting all operable or optimal ranges. As has been discussed supra, Beggs et al, teach an antibody and antibody fragment, comprising F (ab) or Fv fragments that are able to bind to a target site through antibody –antigen binding at conditions lie within physiologically acceptable limits (see entire document , column 1, lines 39-41 and column 2, lines 18-20 in particular). Beggs et al, do not explicitly exemplifies at what specific conditions said antibody of antibody fragments thereof can be eluted from the epitope. However, it is noted that Beggs et al., do not exclude that the bound between antibody or antibody fragment thereof can be broken under second pH of 4.5 and ion strength of 1M NaCl. Moreover, pH of 4.5 and ionic strength of 1m NaCl are well known elution conditions, as taught by Godding et al. In other words, the antibody having specific elution characteristics as recited in the claim 42 was

well known in the art at the time the invention was made. Thus, it would be obvious to one skill in the art that antibody or antibody fragment thereof, taught by Begges et al., would have the functional properties as recited in the claim 42 in the absence of showing of non obvious properties. Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

2. At page 21 of the Brief, Appellant argues that although Cummins et al., teach a physiologically acceptable limits of pH between 6 and 8, a binding pH of 8.5 as recited in the claim 40 does not fall within the physiologically acceptable limits. Appellant further asserts that Cummins et al., does not mention that bound between antibody or fragment thereof is broken at pH of 7.

At page 22 of the Brief, Appellant asserts that Goding reference does not refer to the antibodies of Cummins et al., and thus the cited references cannot established that the antibody of Cummins et al., necessary disassociate at a pH of 7. Appellant further asserts that one of ordinary skill in the art would not reasonable expect the antibodies of Cummins., which binds at physiological conditions to dissociate at pH of about 7.0 but rather at much harsher conditions.

At page 23 of the Brief, Appellant asserts that since dependent claims 2, 9 10, 13-21, 24,27,28,30,31,35 and 43-44 include the elements of independent claim 40 and a prima facie case of

obviousness cannot be established with regard to claim 40, a prima facie case of obviousness also cannot be established with regards to any of said dependent claims.

Appellants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Appellant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This appellant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

In response to appellant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). Moreover, it is noted that Cummins et al do not set a range of physiologically acceptable limits of pH to be between 6 and 8. Cummins et al. teach an monoclonal antibody and fragment thereof to salivary peliicle, which are capable of recognizing cryptitopes . These antibody and fragment thereof are particularly suitable to treat oral cavity (see entire document, Abstract in particular). Cummins et al. teach various binding conditions that lie within physiologically acceptable limits, including pH and ion strength (page 4, lines 38-40 in particular). It is the examiner position that pH 8.5 would be considered by one of ordinary skill in the art to lie within physiological limits. Cummins et al. also teach that antibody and fragment thereof binds diagnostically, therapeutically or cosmetically active substance (see Abstract and pages 3-4 in particular) and can be visualized by using fluorescent labeled antibodies (page 11 in particular). Cummins et al., teach a composition comprising at least one antibody and physiologically acceptable dilutent that is useful as a

cleaning agent (see Example 5 in particular). Cummins et al., teach that diagnostically, therapeutically or cosmetically active substance comprises enzyme such as a proteases, including papain, pepsin, trypsin, ficin and bromelin (page 3, lines 35-55 in particular). Cummins et al. teach the antibody or fragment thereof is capable of binding an epitope of a pathogenic micro-organism (page 3, lines 1-5 in particular) and can be used for teeth bleaching (page 3, lines 3-5 in particular).

Cummins et al., do not explicitly teach that bounds between antibody or fragment thereof and antigen can be broken under specifically chosen conditions for example at pH 7.0, s recited in claim 40. However, it is noted that Cummins et al., do not exclude that the bound between antibody or antibody fragment thereof can be broken under conditions as recited in claims 40. Goding teaches that during optimization of each purification protocol for each antibody of interest and a fragment thereof, the parameters such as pH and ionic strength play an essential role and that it is an inherent properties of all antibody and fragment to bind to an epitope under one set of specifically chosen conditions and be eluted from an epitope (bound of antibody to an epitope is broken) under specifically chosen different conditions. (pages 44-45 in particularly). The examiner disagrees with Appellant's assertion that one skill in the art would not expect that antibody of Cummins et al., would be eluted at pH 7.0. As taught by Goding, it was well known in the art at the time the invention was made , that various elution buffers with various pH including elution with water, i.e. with pH about 7.0 should be used. In other words it was well known in the art of the existence of antibody that can be eluted from the epitope at pH 7.0 Moreover, to preserve the structure of antibody-antigen complex during elution process gentle rather harsh elution condition should be used. Clearly, one skill in the art would consider elution with pH of 7.0 to be a gentle condition. Thus it would be obvious to one skill in the art that antibody or antibody fragment thereof, taught by Cummins et., would have the functional properties as recited in the claim 40 in the absence of showing of non obvious properties. Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In

re Burckel 201 USPQ 67 (CCPA). The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

With regards to the claims 2, 9 10, 13-21, 24,27,28,30,31,35 and 43-44. As has been discussed supra, it is the Examiner position that claim 40 is *prima facie* obviousness in view of the prior art references of record. Thus for at least the same reasons as base claim 40, said claims are also *prima facie* obvious.

At page 25 of the Brief, Appellant argues claim 42 is directed to a selected monoclonal antibodies or fragment thereof that has been selected for its ability to bind epitope at first pH of 8.5. Cummins et al limits the binding of an antibody at physiological pH of 6-8. Appellant further asserts that Cummins et al and Goding references do not teach disassociation conditions at second pH of 4.5 and ion strength of 1 M NaCl.

Contrary to Appellant's assertion, as has been discussed supra, it is noted that Cummins et al., do not set a range of physiologically acceptable limits of pH to be between 6 and 8. Cummins et al. teach an monoclonal antibody and fragment thereof to salivary peliicle, which are capable of recognizing cryptitopes . These antibody and fragment thereof are particularly suitable to treat oral cavity (see entire document, Abstract in particular). Cummins et al. teach various binding conditions that lie within physiologically acceptable limits, including pH and ion strength (page 4, lines 38-40 in particular). It is the examiner position that pH 8.5 would be considered by one of ordinary skill in the art to lie within physiological limits.

With regards to the issue that Cummins et al, do not explicitly exemplifies at what specific conditions, i.e. said antibody of antibody fragments thereof can be eluted from the epitope. It is noted that Cummins et al., do not exclude that the bound between antibody or antibody fragment thereof can be broken under second pH of 4.5 and ion strength of 1M NaCl. Moreover, pH of 4.5 and ionic strength of 1m NaCl are well known elution conditions, as taught by Godding et al. In other words, the antibody having specific elution characteristics as recited in the claim 42 was well known in the art at the time the invention was made. Thus, it would be obvious to one skill in the art that antibody or antibody fragment thereof, taught by Begges et al., would have the functional properties as recited in the claim 42 in the absence of showing of non obvious properties. Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

3. At page 26 of the Brief, Appellant asserts that since dependent claim 29 includes the elements of independent claim 40 and a prima facie case of obviousness cannot be established with regards to claim 40, a prima facie case of obviousness also cannot be established with regards to dependent claim 29. Appellant further asserts that Cole et al. only teach the presence of IgM and IgG antibodies to *Porphyromonas gingivalis*.

As has been discussed supra, it is the Examiner position that claim 40 is *prima facie* obviousness in view of the prior art references of record. Thus for at least the same reasons as base claim 40, claim 29 is also *prima facie* obvious.

The claimed invention differs from the reference teaching only by the recitation of an antibody capable of binding *Porphyromonas gingivalis*.

Cole et al., teach an antibody to *Porphyromonas gingivalis* (see entire document, Abstract in particular) . Cole et al., further teach that this antibody play essential role in the immunopathology of periodontal disease.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the teaching of Cole et al., and those of Beggs et al., and substitute antibody capable of binding to one pathogenic micro-organism associated with periodontal disease with antibody capable of binding with another pathogenic micro-organism associated with periodontal disease.

One of ordinary skill in the art at the time the invention was made would have been motivated do so, because antibody to *Porphyromonas gingivalis* are essential in the immunopathology of periodontal disease and could be used to delivery of the therapeutic agents to the target site as taught by Beggs et al.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

4. At page 27 of the Brief, Appellant asserts that since dependent claim 43 includes the elements of independent claim 40 and a prima facie case of obviousness cannot be established with regards to claim 40, a prima facie case of obviousness also cannot be established with regards to dependent claim 29.

Appellant further asserts that US Patent '511, only teach the existence of monoclonal antibody that binds *Staphylovovvus epidermidis.*

As has been discussed supra, it is the Examiner position that claim 40 is *prima facie* obviousness in view of the prior art references of record. Thus for at least the same reasons as base claim 40, claim 43 is also *prima facie* obvious.

The claimed invention differs from the reference teaching only by the recitation of an antibody capable of binding *Staphylovovvus epidermidis.*

US Patent '511 teach an antibody to *Staphylococcus epidermidis* (see entire document, Abstract in particular) . US Patent '511 further teach that this antibody play essential role in the new therapy for treatment of Staphylococcus infection (see column 4, lines 31-35 in particular

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '511 and those of Beggs et al., and substitute antibody capable of binding to one pathogenic micro-organism associated with periodontal disease with antibody capable of binding with another pathogenic micro-organism associated with periodontal disease.

One of ordinary skill in the art at the time the invention was made would have been motivated do so, because antibody to *Staphylococcus epidermidis* play essential role in the new therapy for treatment of Staphylococcus infection and could be used to delivery of the therapeutic agents to the target site as taught by Beggs et al.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

For the above reasons, it is believed that the rejections should be sustained.

(8) Claims appendix

The Brief contained copy of the claims involved in the appeal.

(9) Evidence Appendix

The following is a listing of the prior art of record relied upon in the rejection of the claims under appeal

1. US Patent 4,138,476
2. US Patent 5,490,988
3. US Patent 5,571,511
4. EP 0736544
5. Weir ed. Immunochemistry, Volume 1, 1986, p38.1-38.15 Blackwell Scientific Publication, Oxford.
6. Goding, Monoclonal Antibodies; Principles and Practice, 1983, Academic. Press, New York. pages 44-45.
7. Cole et al., Immunol. &Infect. Diseases 1993, 3, pages 33-35.
8. Weir ed. Immunochemistry, Volume 1, 1986, p38.1-38.15 Blackwell Scientific Publication, Oxford

(10) Related proceedings appendix

The Brief does not contained any copies of decisions rendered by a court or the Board in any proceeding identified in the related appeals and interferences. Therefore, it is presumed that there are none.

Respectively submitted

Michail Belyavskyi, Ph.D
Art Unit 1644
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Conferees

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Christina Chan
SPE, Art Unit 1644

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Tony Caputa
SPE, Art Unit 1646